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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
MICHAEL WEICKERT, MARC S. GORDON, SANDEEP KUMAR, BING YANG, and RAZAQ SARWAR

Appeal 2007-3221
Application 10/032,239
Technology Center 1600

DECIDED: May 20, 2008

Before TONI R. SCHEINER, DEMETRA J. MILLS, and LORA M. GREEN, *Administrative Patent Judges*.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 40-59, all the claims remaining in the application. The claims stand rejected as obvious over the prior art. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

BACKGROUND

"[P]olyenes such as amphotericin are highly effective antifungal compounds, . . . [but have] very low solubilities in water and in conventional organic solvents such as chloroform . . . Although the solubility . . . can be increased under extreme conditions of pH, such conditions typically lead to significant levels of degradation of drug" (Spec. 3: 24-28).

The present invention is directed to a stable, dry powder composition, suitable for inhalation, containing a polyene antifungal compound.

STATEMENT OF THE CASE

I. Claims 40 and 42-59 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Proffitt (U.S. Patent 5,965,156, issued October 12, 1999) in view of Staniforth (International Patent Application WO 97/03649, published February 6, 1997) and Gordon (U.S. Patent 6,077,543, issued June 20, 2000).

II. Claim 41 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Proffitt, Staniforth, and Gordon, and further in view of Seager (U.S. Patent 4,016,254, issued April 5, 1977).

Claims 40-42, and 50 are representative, and read as follows:

40. A dry powder for delivery by inhalation to the lungs, the dry powder produced by a method comprising:

(i) dissolving a polyene antifungal compound in an acidified solvent to form an acidic polyene-containing solution, and

(ii) spray drying said polyene-containing solution to form an inhaleable dry powder containing no more than about 10% polyene degradation products and characterized by an emitted dose greater than 60%.

41. A dry powder produced by a method comprising:

(i) suspending a polyene antifungal compound in an aqueous solvent to form a suspension,

(ii) wet milling the suspension from (i) to form a wet-milled suspension, and

(iii) spray drying the wet milled suspension to produce an inhalable dry powder containing no more than about 10% polyene degradation products and characterized by an emitted dose greater than about 60%.

42. A spray-dried powder composition suitable for oral inhalation to the lung comprising a therapeutically effective amount of a polyene antifungal compound, wherein the composition comprises no more than about 10% polyene degradation products and is characterized by an emitted dose greater than about 60%.

50. The powder composition of claim 42 substantially comprising neat polyene.

FINDINGS OF FACT (FF)

1. The Specification defines a "dry powder" as "a powdered composition that contains finely dispersed solid particles that are capable of (i) being readily dispersed in an inhalation device and (ii) inhaled by a subject so that a portion of the particles reach the lungs to permit penetration into the alveoli . . . A dry powder . . . is preferably a non-liposomal powder" (Spec. 8: 16-22).

2. According to the Specification, polyene antifungal dry powders effective to penetrate into the alveoli of the lungs have "a mass median diameter (MMD) from about 0.1 to 20 μm. Typically, the MMD of the particles is less than about 10 μm (e.g., ranging from about 0.1 to 10 μm), preferably less than 7.5 μm (e.g., ranging from about 0.5 to 7 microns), and most preferably less than 5 μm, and usually being in the range of 0.1 μm to 5 μm in diameter" (Spec. 24: 19-23). "[T]he powders of the invention are most preferably although not necessarily characterized by extremely small particle sizes, of less than about 2 microns MMD" (Spec. 24: 25-27).

3. According to the Specification, "large particles having diameters above 5 microns are typically removed by impaction in the upper airways (nose, mouth, pharynx, trachea and large bronchi), while those having aerodynamic sizes below 0.5 microns are generally exhaled" (Spec. 25: 13-16).

4. "'Emitted dose' provides an indication of the delivery of a dry powder from the mouthpiece of a suitable inhaler device after a firing or dispersion event . . . the ED is a measure of the percentage of powder which is drawn out of a unit dose package and which exits the mouthpiece of an inhaler device. The ED is defined as the ratio of the dose delivered by an inhaler device to the nominal dose (i.e., the mass of powder per unit dose placed into a suitable inhaler device prior to firing). The ED is an experimentally-determined parameter, and is typically determined in-vitro using a device set up which mimics patient dosing" (Spec. 9: 11-17).

Proffitt

5. Proffitt describes a "lipophilic charge complex of Amphotericin B" (Proffitt, col. 4, l. 27), designed for injection (Proffitt, col. 6, ll. 12-13), in which a "soluble complex is formed between Amphotericin B and distearoylphosphatidylglycerol which has been protonated during dissolution in a solution of chloroform and methanol acidified to a pH of about 1.0 to 3.0. The Amphotericin B-phospholipid complex, while in solution in the small amount of acidified chloroform and methanol, can be mixed with phosphatidylcholine and cholesterol and reproducibly spray dried under controlled conditions to yield a lipid powder which is readily processed into liposomes, using an aqueous buffer solution having a pH such that the pH of

the final solution is below about 5.5, preferably between about 4.5 and 5.5" (Proffitt, col. 4, ll. 36-47).

6. In Proffitt's Example I, a formulation containing amphotericin B, distearoylphosphatidylglycerol, hydrogenated egg phosphatidylcholine, and cholesterol in a molar ratio of 0.4 : 0.8 : 2.0 : 1.0 was spray dried, resulting in a "free flowing yellow to light orange powder" suitable for storage (Proffitt, col. 7, l. 45 to col. 8, l. 60). The spray dried powder was rehydrated to form a liposome preparation with a mean liposome diameter of 38.3 nm (0.0383 μm) (Proffitt, col. 8, ll. 40-54).

7. According to Proffitt, "the Amphotericin B-lipid complex is highly stable and has a high affinity for the lipid bilayer into which it becomes inserted. The result is a decrease in acute toxicity" (Proffit, col. 7, ll. 15-17). "Furthermore, the associated complex is highly stable during storage" (Proffitt, col. 7, ll. 37-38).

Staniforth

8. According to Staniforth, "[f]or effective delivery of active particles deep into the lungs, the active particles should be small, with an equivalent aerodynamic diameter substantially in the range of 0.1 to 5 μm . . . Small particles are, however, thermodynamically unstable due to their high surface to volume ratio, which . . . encourages particles to agglomerate . . . result[ing] in the active particles leaving the inhaler as large stable agglomerates or being unable to leave the inhaler" (Staniforth 2: 12-25). "If those agglomerates do not break up when the powder is inhaled, they are unlikely to reach the lower lung due to their size" (Staniforth 4: 20-22).

9. Staniforth teaches that an anti-adherent material, e.g., leucine, should be added to the powder "to hinder the formation of stable agglomerates of the active material" (Staniforth 4: 12-14). On the other hand, "it is favourable for unstable agglomerates of particles to be present in the powder when it is in the inhaler device" (Staniforth 5: 11-13), since unstable agglomerates large enough to leave the inhaler, are "likely to be broken down efficiently in the turbulent airstream created on inhalation" (Staniforth 5: 14-27).

10. Staniforth does not mention polyene antifungal compounds.

Gordon

11. Gordon describes a method for preparing spray dried compositions containing combinations of hydrophobic drugs (e.g., amphotericin B), and hydrophilic excipients (Gordon, col. 5, ll. 21-26 and 54). The method produces ultrafine dry powders, suitable for oral inhalation, with an average particle sizes preferably ranging from 0.4 to 5 μm" (Gordon, col. 5, ll. 8-20).

12. According to Gordon, the success of the method "relies on proper selection of the liquid medium or media for solubilizing the hydrophobic drug . . . and hydrophilic excipient . . . as well as on the manner of introducing the component to the spray dryer" (Gordon, col. 8: 36-40).

13. Gordon does not describe the liquid medium or media appropriate for solubilizing amphotericin B.

Seager

14. Seager teaches that wet milling can be used to finely divide particles of medicaments and excipients in suspension prior to spray drying (Seager, col. 8, l. 66 to col. 9, l. 5).

14. Seager does not mention polyene antifungal compounds.

DISCUSSION

The Rejection of Claims 40 and 42-59

The Examiner rejected claims 40 and 42-59 as unpatentable over Proffitt, Staniforth, and Gordon.

According to the Examiner, Proffitt teaches that "amphotericin B is useful for treating fungal infections" (Ans. 3), and describes "amphotericin liposome powder[s] with diameters less than 2 um, which may be obtained through a spray drying of an acidified solution of amphotericin. The powders [are] characterized as stable and less toxic" (Ans. 3). The Examiner acknowledges that Proffitt "does not teach expressly a powder contain[ing] . . . amphotericin, which is for inhalation" (Ans. 4).

The Examiner cites Staniforth as teaching that "[t]he optimal particle size for lung inhalation administration is 0.1 um to 5 um" (Ans. 4), and that "powder composition[s] for inhalation generally compris[e] high concentration[s] of active ingredient (e.g., 60% or higher by weight)" (*id.*), and may include leucine, as an "anti-adherent material" (*id.*).

Finally, the Examiner cites Gordon as teaching that "hydrophobic drugs for lung delivery, such as amphotericin B are known to be made into particles less than 5 um in size" (Ans. 4).

The Examiner contends that "making a powder composition suitable for inhalation (i.e., with certain size of the particle) administration, or controlling degradation of the active ingredient during the process of making, is a matter of optimization of a result effective variable" (Ans. 4), and "method[s] of making such powders [are] well-known in the art" (*id.*). The Examiner concludes that "it would have been prima facie obvious"

(Ans. 4), and "[a] person of ordinary skill in the art would have been motivated to make a stable amphotericin powder composition for inhalation administration by drying a[n] acidified solution of amphotericin according to Proffitt's method (without adding the other ingredients required for the liposome composition)" (Ans. 4), "because Proffitt's method is known to provide [a] stable amphotericin composition" (*id.*).

Appellants argue essentially that Proffitt does not disclose or suggest an inhalable dry powder containing no more than about 10% polyene degradation products and characterized by an emitted dose greater than 60% (App. Br. 11), and the teachings of Staniforth and Gordon "would not suggest a modification of Proffitt . . . that arrives at the presently claimed invention" (*id.*).

We agree with Appellants that the Examiner's conclusory statements do not provide an adequate factual basis, or a rational underpinning, to support the legal conclusion of obviousness. *See In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"); *accord KSR International Co., v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) (noting in order to facilitate review of the obviousness determination, the "analysis should be made explicit.").

The rejected claims are directed to polyene powders suitable for delivery to the lungs by inhalation; in addition, as pointed out by Appellants, all of the claims (with the exception of claim 57, which the Examiner has not specifically addressed) require that the powders contain no more than 10%

polyene degradation products, and are characterized by an emitted dose greater than 60% (*see* FF 4) (*not*, we note, a concentration of active ingredient higher than 60%, which is what the Examiner apparently focused on (Ans. 4, ¶ 5)). None of these limitations are adequately addressed by the Examiner's assertion that "making a powder composition suitable for inhalation" and "controlling degradation of the active ingredients" (Ans. 4) is a matter of optimizing result effective variables. First, "making a powder . . . suitable for inhalation" and "controlling degradation" are not *variables*, as implied by the Examiner. They are *results*, which are *effected*, (i.e., accomplished or produced) by manipulating certain variables (e.g., pH, solvent, temperature, etc.). The Examiner has not identified anything in the references that teaches which variables will accomplish the required results.

In any case, Proffitt describes an *injectable* formulation of a polyene (amphotericin B) (FF 5), and attributes its stability and decreased toxicity to its association with phosphatidylglycerol, phosphatidylcholine, and cholesterol (FF 7). The Examiner has not identified anything in Staniforth (a reference directed to anti-agglomeration compounds, which does not even mention polyenes (FF 9, 10)) that would have suggested varying Proffitt's formulation in the manner proposed by the Examiner, i.e., making Proffitt's formulation "without adding the other ingredients required for the liposome composition" (Ans. 4). Similarly, the Examiner has not identified anything in Gordon that would have suggested varying Proffitt's formulation in the manner proposed.

To the extent the Examiner alternatively (and belatedly) asserts that "Proffitt teaches dried monohydrated powders [in Example 1] . . . Therefore,

Proffitt's method is suitable for mak[ing] aerosol dried powder" (Ans. 6), we find that the Examiner has not established any factual basis for this assertion. That is, the Examiner has not established that the amphotericin-containing powder described in Example I of Proffitt (which additionally contains distearoylphosphatidylglycerol, hydrogenated egg phosphatidylcholine, and cholesterol (FF 6)) is suitable for oral inhalation, contains no more than 10% polyene degradation products, and is characterized by an emitted dose greater than 60%.

Accordingly, the Examiner's rejection of claims 40 and 42-59 as unpatentable over Proffitt, Staniforth, and Gordon is reversed.

The Rejection of Claim 41

The Examiner rejected claim 41 as unpatentable over Proffitt, Staniforth, and Gordon, and further in view of Seager.

According to the Examiner, Proffitt, Staniforth, and Gordon, "take[n] together do not teach expressly the employment of aqueous suspension, wet milling and spray drying to make the powder" (Ans. 5), but "it would have been obvious . . . to employ wet milling-spray drying technique for making a powder because such technique is well known in the art for making fine particles" (*id.*).

This rejection suffers from essentially the same infirmities as the first rejection.

Accordingly, the rejection of claim 41 as unpatentable over Proffitt, Staniforth, Gordon, and Seager is reversed.

SUMMARY

Both of the Examiner's rejections of the claims as unpatentable under 35 U.S.C. § 103(a) are reversed.

REVERSED

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